Janssen Pharmaceutical K.K.

Statistical Analysis Plan

A Phase 2/3, Multicenter, Randomized, Open-label, Active-controlled Study to Evaluate the Efficacy and Safety of Bedaquiline Administered as Part of a Treatment Regimen With Clarithromycin and Ethambutol in Adult Patients With Treatment-refractory Mycobacterium Avium Complex-lung Disease (MAC-LD)

Protocol TMC207NTM3002; Phase 2/3

(TMC207) Bedaquiline

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout this document to represent Janssen Pharmaceutical K.K. in Japan.

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	26 February 2021	Not Applicable	Initial release
2	25 April 2022	• Appendix 11 (Unblinding Plan), Appendix 12 (Agreement on the Unblinded Information Handling) and Appendix 13 (Running Log of Default Unblinders) were added. • The definition of culture reversion (relapse or reinfection) was added in Section 5.5.2. • Other changes were made to keep consistency with the protocol.	• Detailed unblinding plan which was added in the protocol Amendment 6. • Clarified the definition of culture reversion.
3	24 May 2024	• Appendix 11 (Unblinding Plan) and Appendix 12 (Agreement on the Unblinded Information Handling) were updated. • Region and duration of previous therapy for MAC-LD were added in Appendix 3 (Demographics and Baseline Characteristics). • Other changes were made to keep consistency with the protocol and correct errors.	• Clarified unblinders and scope of blinding. • Reflected study design changes from protocol Amendment 7 to Amendment 8.
4	31 January 2025	1. Definition of analysis phase was modified to include data after switching to individualized treatment regimen in the investigational phase. 2. Visit window for optional cohort was modified to use the start date of optional treatment as baseline. 3. Region (Japan, non-Japan) was added as a stratification factor in statistical tests. 4. The supplementary estimand considering for treatment non-compliers was deleted. 5. Other changes were made for clarification, error correction or consistency with other study documents.	1. Investigational treatments are included in individualized treatment regimen. 2. Variable washout period before start of optional treatment is considered. 3. Based on the advice from PMDA. 4. All subjects are compliers defined as 80% or more compliance.

1. INTRODUCTION

This statistical analysis plan (SAP) for the TMC207NTM3002 phase 2/3 trial describes the statistical analyses and definitions to evaluate the efficacy and safety of Bedaquiline(BDQ) administered as part of a treatment regimen with Clarithromycin and Ethambutol in adult patients with treatment-refractory Mycobacterium Avium Complex-lung Disease (MAC-LD).

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Microbiological assessment in MGIT: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT at Week 24.
Secondary	
• Microbiological assessment in 7H10 or 7H11 agar media: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in 7H10 or 7H11 agar media at Week 24.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Change from baseline in patient-reported health status on total score of SGRQ at Week 24.
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD up to Week 48.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media at Week 48. • Percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media, respectively, at each visit after Week 2 per Schedule of Activities. • Time to sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT up to Week 48. • Time to positivity in MGIT up to Week 48.

Objectives	Endpoints
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Change from baseline in patient-reported health status on total score of SGRQ at Weeks 48 and 60. • Change from baseline in lung function parameters at Weeks 24, 48, and 60. • Percentage of participants who undergo a change in their MAC-LD treatment regimen by Week 24, by Week 48 (Group A) and by Week 60 (Group B).
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 60.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media at Week 60.
• To evaluate the safety and tolerability of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Safety and tolerability based on assessment of AEs, clinical laboratory assessments, 12-lead ECG, vital signs, physical examination, visual examination, and audiology up to Week 60.
• To evaluate the PK of BDQ (and metabolite M2), and CAM (and metabolite 14-OH-CAM [optional]).	• PK exposures of BDQ (and metabolite M2 [optional]) at Day 1, Weeks 2, 8, 12, 24, and 48, and CAM (and metabolite 14-OH-CAM [optional]) at Day 1, Weeks 2, 8, 12, and 24.
Exploratory	
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment refractory MAC - LD assessed by QOL-B NTM module.	• Change from baseline in patient reported health status on score of QOL-B NTM module at Weeks 24, 48, and 60.
• To evaluate the occurrence of culture reversion (relapse or reinfection) in participants who previously had sputum conversion.	• Rate of culture reversion (relapse or reinfection) up to Week 60.
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Percentage of participants having MAC isolates with acquired resistance to CAM detected by a phenotypic method up to Week 60. • Percentage of participants having MAC isolates with increased MICs to BDQ (at least 4 fold increase) up to Week 60.

Objectives	Endpoints
• To evaluate PK/PD relationships for safety and efficacy of BDQ (and CAM [optional]).	• Exposure, and safety and efficacy (PK/PD) relationship assessments of BDQ (and CAM [optional]) by Week 24.
• To determine the mechanisms of resistance in participants' MAC isolates with increased BDQ MICs by sequencing both *atpE, mmpT5* and other genes (if available).	• Evolution of the *atpE, mmpT5* and other gene sequences up to Week 60.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB for participants who achieved sputum culture conversion (at Weeks 24, 48, and 60).	• Change from baseline in patient-reported health status on total score of SGRQ at Weeks 24, 48, and 60. • Change from baseline in patient reported health status on score of QOL-B NTM module at Weeks 24, 48, and 60. • Change from baseline in lung function parameters at Weeks 24, 48, and 60. • Change from baseline in chest CT findings at Weeks 24, 48, and 60.

1.2. Study Design

This is a multicenter, randomized, open-label, active-controlled study to evaluate efficacy and safety of BDQ compared with rifamycin administered as part of a treatment regimen with clarithromycin (CAM) and ethambutol (EB) for 48 weeks in adult participants with treatment-refractory MAC-LD defined as participants who are sputum culture positive for MAC despite at least 6 months of MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within the last 12 months. The study will consist of a screening period of 70 days (10 weeks) (including rifamycin washout period of 14 days for participants to whom this is applicable), an open-label treatment period of 48 weeks (baseline visit [Day 1] to Week 48) in Treatment Group A [Group A] or 60 weeks (Day 1 to Week 60) in Treatment Group B [Group B], and follow-up period of 12 weeks in Group A. Participants will return for study visits biweekly in the first 12 weeks, and then every 4 weeks until Week 60. In addition, this study provides an option to receive BDQ-containing regimen for nonconverters in Group B based on the result of microbiological test up to Week 24 as the optional cohort.

Participants who meet all the eligibility criteria will be randomized in a 1:1 (Group A: Group B) ratio stratified by country:

- Group A: BDQ + CAM + EB
- Group B: rifamycin (rifampicin [RFP] or rifabutin [RBT]) + CAM + EB

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

A futility analysis will be implemented to evaluate early the benefit/risk balance by assessing safety and efficacy in the first 60 participants (about 30 participants from both groups) who reach the Week-24 time point or discontinued earlier, or switched to individualized treatment regimen. This futility analysis is nonbinding and the IDMC will recommend the continuation or termination of the study based on the whole package of information, which also includes other efficacy and safety assessments. Sponsor will decide the continuation or termination of the study based on the recommendation by IDMC.

Blinding

Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The investigator and participant will be blinded for microbiological assessments until each participant has completed the other assessments at Week 24. If during the treatment period, the participant presents with clinical worsening, unblinding for microbiology assessments is allowed at the discretion of the investigator.

As this is an open-label study, blinding procedures are not applicable. However, the microbiological results from Week 2 to Week 24 will be blinded to the investigators, site staffs and participants until the completion of the other assessments at Week 24 by the investigators. In case the investigators need to know the microbiological result to decide if participants should be switched to an individualized treatment regimen or continue the study treatment regimen, due to clinical worsening, the investigators can access the microbiological result from the central laboratory (for the detailed procedure, refer to the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test). Sponsor except for specific personnel listed below must keep the blinding of all the microbiological assessment after Week 2 until unblinding takes place for the primary analysis.

In addition, sponsor personnel involved in monitoring of the study sites and personnel involved in management operation of the central laboratory etc. are excluded from maintenance of blinding for microbiology assessments, taking into account that sponsor needs to confirm that investigators and etc. comply with the protocol and the decision to switch to individualized treatment regimen and the optional cohort is made based on the appropriate process. Details will be provided in Appendix 11 (Unblinding Plan).

2. STATISTICAL HYPOTHESES

The hypothesis of this study is that BDQ-containing regimen is superior to rifamycin-containing regimen and increases the proportion of participants with sputum culture conversion in mycobacteria growth indicator tube (MGIT) at Week 24 as compared to rifamycin-containing regimen.

3. SAMPLE SIZE DETERMINATION

Based on the results of 2 clinical studies in AMK liposome inhalation suspension (ALIS, Arikayce®), (Phase 2 [Griffith 2018] and Phase 3 [Olivier 2017]) in an analogous population, it is

anticipated that the rifamycin-containing regimen in this study will have a sputum culture conversion rate assumed to be equal to 10% after 24 weeks of treatment.

A sample size of 124 participants (62 in Group A: the BDQ containing regimen, 62 in Group B: the rifamycin-containing regimen) will have a power of about 80% to show superiority for a 20% difference in proportion of participants having sputum conversion at Week 24 based on a chi-square test (at the 5% 2-sided significance level) on the intent-to-treat (ITT) population.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	**Description**
Enrolled	All participants who sign the ICF
Randomized	The randomized analysis set includes all participants who were randomized in the study. Participants will be analyzed according to the study intervention they were randomly assigned to.
Intent-to-treat (ITT)	All randomized participants who were randomly assigned to an intervention arm and who take at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they were randomly assigned to. ITT will be the primary population for efficacy analyses.
Safety	The safety analysis set includes all participants who received at least 1 dose of the study intervention. Participants will be analyzed according to the study intervention they actually received.
Pharmacokinetics (PK) Analysis Set	The PK analysis set is defined as participants, regardless of their compliance with the protocol, who received at least 1 dose of the study intervention and have at least 1 valid blood sample drawn for PK analysis.
Pharmacokinetic/pharmacodynamic (PK/PD) Analysis Set	QTcF will be selected for safety parameter. MAC LD treatment outcome will be selected for efficacy parameter. The PK/PD analysis set includes all subjects who received at least 1 dose of BDQ and/or CAM, and have at least 1 time point with nominal time-matched plasma concentration and safety or efficacy parameter.

5. STATISTICAL ANALYSES

5.1. General Considerations

The SAP will use throughout the document the following definition

- Study intervention refers to: Bedaquiline or rifamycin
- Study intervention arm refers to:
    - Group A: BDQ + CAM + EB
    - Group B: rifamycin (RFP or RBT) + CAM + EB

Baseline

In general, the baseline assessment is defined as the last observed nonmissing measurement before the date and time of the first administration of any of study treatments. For optional cohort, the baseline assessments are defined as follows.

- Microbiological endpoints: Assessments at Week 24.
- Other endpoints: The last observed nonmissing measurement before BDQ administration.

In case the first administration time is missing, the first observed measurement on Day 1 will be used as the baseline measurement. If no observed measurement on Day 1, the last observed measurement before Day 1 will be used as the baseline assessment.

Analysis Phase

Analysis phase	**Start date**	**End date**
Screening	The date of signing the informed consent	1 day before the first study intervention intake
Investigation	Date of the first study intervention intake	If the participants are from Group A, Min [Week 48, study discontinuation] If the participants from Group B will not convert to the optional cohort, Min [Week 60, study discontinuation]
		If the participants will convert to the optional cohort, 1 day before the optional investigation phase
Optional investigation	Date of the first BDQ+CAM+EB intake for nonconverters came from Group B	For nonconverters came from Group B, Min [Optional Week 48, study discontinuation]
Follow-up	If the participants are in Group A and moved to follow-up period, end of the investigation phase + 1 day	Min [Week 60, study discontinuation]

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 60 of the open-label phase or at OPW48 of the optional cohort. Following completion of the study, the participant may continue the SOC per Japanese guidelines or medical practice at each study site for at least 1 year after culture conversion, at the discretion of the investigator.

Missing and Partial Dates Imputation Rules

For analysis and reporting purposes, missing or partial dates in adverse event (AE onset date; AE end date), diagnosis and infection dates, concomitant therapies (start date; end date) and NA/IFN prior to baseline/study entry dates will be imputed according to the rules in the following subsections. The original, nonimputed, dates will be used only in listings.

Adverse Event Onset Date and Resolution Date

Partial AE onset dates will be imputed as follows:

- If the AE onset date is missing the day only, it will be set to:
    - The first day of the month when the AE occurred, if month/year of the AE onset date is different than the month/year of the first administration of study treatment date.
    - The day of the first study treatment administration, if the month/year of the AE onset date is the same as the month/year of the first study treatment administration but the month/year of the AE resolution date is different.
    - The earliest between the day of the first study treatment administration date and day of AE resolution date, if month/year of the AE onset are the same as both the month/year of the first study drug administration and the AE resolution date.
- If the AE onset date is missing both day and month, it will be set to the earliest of:
    - January 1 of the year of onset, as long as this date is on or after the first study drug administration.
    - Month and day of the first study treatment administration, if this date is in the same year of AE onset date.
    - December 31 if the AE onset date year is prior to the year of the first study drug administration.
    - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing the day only, it will be set to the earliest of the last day of that month or the day of the date of death, if the participant died in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of that year or the day and month of the date of death, if the participant died in that year.
- Completely missing resolution dates will not be imputed.

MAC-LD Diagnosis Dates

If the reported date is partially missing, the following imputation rules will be applied:

- the 15th of the month, if only the day is missing.
- the 30th of June, if only the year is available.
- No imputation if completely missing.

Concomitant Medication Dates

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied:

- the 15th of the month, if only the day is missing.
- the 30th of June, if only the year is available.
- if the imputed start date is after the concomitant medication end date, further adjustment of the imputed start date is required. It will be imputed as the concomitant medication end date
- No imputation if completely missing.

If the medication was taken prior to study start (Day 1) based on eCRF question, and the imputed start date is after first treatment date, further adjustment of the imputed start date is required. It will be imputed as the day prior to first dosing date.

If the medication was taken after study start (Day 1) based on eCRF question, and the imputed start date is prior to first dosing date, the imputed start date will be further adjusted to be the first study treatment dosing date. The partially missing medication end date will be imputed following the rule described at the beginning of this section to ensure it is on or after first dosing date, and after its start date.

In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial, unless the eCRF indicating that the medication was taken after study start.

In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial, unless the eCRF indicating not ongoing.

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2 and Table 3) are the analysis visit windows and the target days for each visit defined in the protocol.

Start date in the investigation phase is defined as the date of first study intervention intake. All efficacy and safety assessments during the investigation phase will be assigned an analysis study day relative to this date.

The investigation phase study day in the investigation phase (ADY) is defined as:

ADY = visit date – investigation phase start date + 1

For visits on or after investigation phase Day 1, and

ADY = visit date – investigation phase start date

For visit before investigation phase Day 1 (screening phase).

The optional investigation phase study day in the optional investigation phase (ADY) is defined as:

ADY = visit date - optional investigation phase start date + 1

For visits on or after optional investigation phase Day 1.

All efficacy and safety assessments during the Follow-up (FU) phase will be assigned a day relative to FU start date. The FU study day in the FU treatment phase (ADY) is defined as:

FU ADY = visit date – FU start date + 1

Table 2: Visit Windows of Group A/B

Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Screening phase	1	Screening	<1	[-56,0]
Investigation phase	2	Baseline	1	1
	3	Week 2	[2,22]	15
	4	Week 4	[23,36]	29
	5	Week 6	[37,50]	43
	6	Week 8	[51,64]	57

Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
	7	Week 10	[65,78]	71
	8	Week 12	[79,99]	85
	9	Week 16	[100,127]	113
	10	Week 20	[128,156]	141
	11	Week 24	[157,184]	169
	12	Week 28	[185,212]	197
	13	Week 32	[213,240]	225
	14	Week 36	[241,268]	253
	15	Week 40	[269,296]	281
	16	Week 44	[297,324]	309
	17	Week 48	[325,352]	337
Follow-up phase (Group A)/ Investigation phase (Group B)	18	Week 52	[353,380]	365
	19	Week 56	[381,406]	393
	20	Week 60	[407,425]	421

*Relative to the date of starting dose in investigation phase

Table 3: Visit Windows of the Optional Cohort

Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Optional Investigation phase	2	Optional Baseline	1	1
	3	Optional Week 2	[2,22]	15
	4	Optional Week 4	[23,36]	29
	5	Optional Week 6	[37,50]	43
	6	Optional Week 8	[51,64]	57
	7	Optional Week 10	[65,78]	71
	8	Optional Week 12	[79,99]	85
	9	Optional Week 16	[100,127]	113
	10	Optional Week 20	[128,156]	141
	11	Optional Week 24	[157,184]	169
	12	Optional Week 28	[185,212]	197
	13	Optional Week 32	[213,240]	225
	14	Optional Week 36	[241,268]	253
	15	Optional Week 40	[269,296]	281
	16	Optional Week 44	[297,324]	309
	17	Optional Week 48	[325,352]	337

*Relative to the date of starting dose in optional investigation phase

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention
- Participants who discontinued study
- Participants who switched to the optional cohort

- Participants who switched to the individualized treatment regimen
- Reasons for discontinuation of study intervention
- Reasons for discontinuation of study

Listings of participants (eg, the date of last study visit, the last study phase and week, the date of discontinuation and the reason) will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who discontinued study
- Participants who were randomized yet did not receive any study interventions.

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint

The primary endpoint of this study is Sputum Culture Conversion in MGIT at Week 24. Sputum culture conversion is defined as 3 consecutive negative sputum cultures taken at least 25 days apart based on actual collection dates. Sputum cultures at unscheduled visits will also be used for the determination of sputum culture conversion.

5.3.2. Primary Estimand

The main clinical quantity of interest to be estimated in this study, is defined by the following 5 components:

- Population: Adult patients with treatment-refractory MAC-LD
- Endpoint: Proportion of participants with sputum culture conversion (sputum culture conversion rate) in MGIT at Week 24.
- Treatment: BDQ-containing regimen versus rifamycin-containing regimen.
- Population Level Summary: The difference of proportions between treatment groups.
- Intercurrent Events (ICE):
  a. Deaths, treatment discontinuation and treatment regimen changes prior to Week 24: all these ICEs will be handled by a composite strategy to treat the participants as nonconverters.
  b. Major protocol deviations (besides treatment regimen changes prior to Week 24): all data will be used regardless of the occurrence of major protocol deviations (treatment policy strategy).

5.3.2.1. Main Estimator of the Primary Estimand

Assumptions

- Missing not at random: missing data due to deaths, treatment discontinuation and treatment regimen changes will be treated as nonconversion.

- No prognostic factors for the proportion of converters.

Data Included

All randomized participants who take at least 1 dose of study intervention will be used.

Missing Data Handling Rule

A contaminated or missing sputum culture occurring between two negative cultures will be interpreted as "no data" and will not contribute to the assessment of the 3 consecutive negative cultures.

Table 4 shows how to judge the response at Week 24 with considering missing samples or contaminated sputum cultures.

Table 4: Cases of Sputum Culture Conversion

Week 8	Week 10	Week 12	Week16	Week 20	Week 24	Converter?
Neg/Pos	Neg/Pos	Neg	Missing	Neg	Neg	Yes
Neg/Pos	Neg/Pos	Neg	Neg	Missing	Neg	Yes
Neg/Pos	Neg/Pos	Neg	Neg	Neg	Missing	Yes
Neg	Neg	Neg	Missing	Missing	Neg	Yes
Pos	Neg	Neg	Missing	Missing	Neg	No
Neg	Pos	Neg	Missing	Missing	Neg	No

*Missing includes the missing samples and contaminated sputum culture.

Analysis Methods

Cochran-Mantel-Haenszel test stratified by region (Japan, non-Japan) at the 5% 2-sided significance level will be used to compare sputum culture conversion rate in MGIT at Week 24. The proportion of the participants with sputum culture conversion at Week 24 will be summarized as randomized and the stratum adjusted treatment difference with 2-sided 95% CI will also be presented.

5.3.2.2. Sensitivity Estimator of the Primary Estimand

Assumptions

- Missing not at random: missing data due to deaths, treatment discontinuation and treatment regimen changes will be treated as nonconversion.

- The type of MAC (*M. avium, M. intracellulare and M. avium + M. intracellulare*) is a possible prognostic factor for the proportion of converters.

Data Included

Same as the main estimator.

Missing Data Handling Rule

Same as the main estimator.

Analysis Methods

Cochran-Mantel-Haenszel test stratified by the type of MAC (*M. avium* only or other) at the 5% 2-sided significance level will be used to compare sputum culture conversion rate in MGIT at Week 24. The proportion of the participants with sputum culture conversion at Week 24 will be summarized as randomized and the stratum adjusted treatment difference with 2-sided 95% CI will also be presented.

5.3.3. Supplementary Estimand

The supplementary estimand is defined with considering treatment regimen change under treatment policy strategy.

- Population: Adult patients with treatment-refractory MAC-LD
- Endpoint: Proportion of participants with sputum culture conversion in MGIT at Week 24.
- Treatment: BDQ-containing regimen versus rifamycin-containing regimen.
- Population Level Summary: The difference of proportions between treatment groups.
- Intercurrent Events (ICE):
  a. Deaths and treatment discontinuation will be handled by a composite strategy to treat the participants as nonconverters.
  b. Treatment regimen change prior to Week 24: if the participant change treatment regimen prior to Week 24 but microbiology assessments are available at that time point, all data will be used regardless of occurrence of the intercurrent event (treatment policy strategy).

  Major protocol deviations (besides treatment discontinuation prior to Week 24): all data will be used regardless of the occurrence of major protocol deviations (treatment policy strategy).

5.3.3.1. Main Estimator of the Supplementary Estimand

Assumptions

Same as for the main estimator of the primary estimand.

Data Included

All randomized participants who take at least 1 dose of study intervention will be used.

Missing Data Handling Rule

Same as for the main estimator of the primary estimand.

Analysis Methods

The Cochran-Mantel-Haenszel test stratified by region (at the 5% 2-sided significance level) will be used to compare sputum culture conversion rate in MGIT at Week 24. The proportion of the subjects with sputum culture conversion at Week 24 will be summarized as randomized and the treatment difference with 2-sided 95% CI will also be presented.

5.3.4. Subgroup Analyses of Primary Efficacy Endpoint

All categorical variables described in Section 6.3 will be used for subgroup analysis, and the treatment difference of proportion of the subjects with sputum culture conversion will be presented with 95% CI. The subgroup analysis will be applied for the primary estimand.

5.4. Secondary Endpoints Analysis

5.4.1. Key Confirmatory Secondary Endpoints

No key confirmatory secondary endpoints are defined in this study.

5.4.1.1. Definition of Endpoints

Not applicable.

5.4.1.2. Estimands

Not applicable.

5.4.1.3. Analysis Methods

Not applicable.

5.4.2. Supportive Secondary Endpoints

5.4.2.1. Definition of Endpoints

Sputum culture conversion in MGIT and 7H10 or 7H11 agar media

The definition of sputum culture conversion is described in Section 5.3.1.

Sputum culture negativity in MGIT and 7H10 or 7H11 agar media

The percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media will be calculated at each visit after Week 2, respectively. No imputation rules will be applied for withdrawn and missing data.

Time to sputum culture conversion in MGIT

For this time-to-event analysis, an event is defined as sputum culture conversion in MGIT. The definition of sputum culture conversion is described in Section 5.3.1.

The date of event is defined as the date of the first of 3 consecutive negative sputum cultures taken at least 25 days apart. For subjects who achieve culture conversion after switching to individualized treatment regimen, the culture conversion after switching will not be treated as an event.

The rules of censoring are as follows.

Analysis period	Rules of censoring
From Day 1 to Week 24	● If study discontinuation before event, date of censoring will be study discontinuation date. ● If no study discontinuation and no event, date of censoring will be the last sputum culture test date.
From Day 1 to Week 48	● If switching to optional cohort before event, date of censoring will be the last sputum culture test date before switching to optional cohort. ● If study discontinuation before event, date of censoring will be study discontinuation date. ● If no switching to optional cohort and no study discontinuation and no event, date of censoring will be the last sputum culture test date.
From Optional Day 1 to Optional Week 48 (only for subjects who switched to Optional Cohort)	● If study discontinuation before event, date of censoring will be study discontinuation date. ● If no study discontinuation and no event, date of censoring will be the last sputum culture test date.

Time to positivity in MGIT

Time to positivity is calculated as the time required to positive signal in MGIT. If the qualitative result is "Negative", time to positive signal is set to 42 (days). No imputation rules will be applied for withdrawn and missing data. If there are multiple positive samples, mean value will be used.

St. George's Respiratory Questionnaire (SGRQ)

The SGRQ responses are used to assess the subjects' quality of life by evaluating 3 health domains: symptoms (Part1), and activity and impacts (both Part 2). Higher domain scores indicate more limitations. The composite total score is derived from the 3 domain scores. Each domain score and the total score has a range of 0 to 100, with 0 indicating the best possible quality of life. For treatment comparison at Week 24, if a part of score is missing at Week 24, the imputation rule will be applied based on SGRQ manual (VTMF-10523342).

Lung function parameters

The lung function parameters including forced expiratory volume in one second, forced vital capacity, inspiratory capacity, functional residual capacity, and total lung capacity, will be assessed.

5.4.2.2. Analysis Methods

5.4.2.2.1. Sputum Culture Conversion in 7H10 or 7H11 Agar Media

Sputum culture conversion at Week 24: The Cochran-Mantel-Haenszel test stratified by region (at the 5% 2-sided significance level) will be used to compare sputum culture conversion rate in MGIT at Week 24. The proportion of the subjects with sputum culture conversion at Week 24 will be summarized as randomized and the treatment difference with 2-sided 95% CI will also be presented. The definition of sputum culture conversion is described in Section 5.3.1.

Sputum culture conversion at Week 48 and Week 60: The proportion of participants who achieved sputum culture conversion of each treatment group (ie, as randomized) will be calculated with 95% CI. Participants requiring a treatment regimen change to individualized regimen will also be considered as nonconverters.

5.4.2.2.2. Sputum Culture Conversion in MGIT

The percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT will be summarized by randomized treatment group through Week 24. After Week 24, the percentage of participants with sputum culture conversion in optional cohort will be also summarized.

Sputum culture conversion at Week 48 and Week 60: The percentage of participants who achieved sputum culture conversion at Week 24 and completed 48-week BDQ-containing regimen and achieved sputum culture conversion at Week 60 in Group A will be compared with the percentage of participants who completed 60-week standard of care(SOC) regimen and achieved sputum culture conversion at Week 60 in Group B using the Cochran-Mantel-Haenszel test stratified by region. For treatment regimen change prior to the analysis timepoints, both the strategies similar to the primary estimand and the supplementary estimand for the primary endpoint will be applied.

5.4.2.2.3. Sputum culture negativity in MGIT and 7H10 or 7H11 agar media

The percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media will be also summarized at each visit after Week 2, respectively. After Week 24, the percentage of participants with sputum culture conversion in optional cohort will be also summarized.

Sputum culture negativity in MGIT at Week 24: The Cochran-Mantel-Haenszel test stratified by region (at the 5% 2-sided significance level) will be used to compare sputum culture negativity in MGIT at Week 24. The proportion of the subjects with sputum culture negativity at Week 24 will be summarized as randomized and the treatment difference with 2-sided 95% CI will also be presented. A generalized linear model including treatment, region (Japan, non-Japan), time, and treatment-by-time interaction terms will be applied for the number of negative participants and the number of all participants at each timepoint and comparison between treatment groups will be performed using the appropriate contrast for the percentage of negative participants at Week 24. If the subjects switch to individualized treatment regimen or to optional cohort, sputum culture should be considered as not negative.

5.4.2.2.4. Time to sputum culture conversion in MGIT

Kaplan-Meier estimates will be produced for the time to sputum culture conversion. The percentage of the number of the subjects with sputum culture conversion will be presented by treatment groups as randomized. The definition of the event is described in Section 5.4.2.1.

Kaplan-Meier curves will be also graphically presented. The difference between the treatment groups will be compared using the log-rank test stratified by region (Japan, non-Japan) for the time to sputum culture conversion up to Week 24.

5.4.2.2.5. Time to positivity in MGIT

Time to positivity will be descriptively presented by visit for the patients with positivity of sputum culture. The descriptive statistics will be summarized by treatment groups. For the subjects who switch from RFP-containing regimen to BDQ-containing regimen, time to positivity after Week 24 will be also summarized.

5.4.2.2.6. St. George's Respiratory Questionnaire (SGRQ)

The changes from baseline in total score of SGRQ and domain scores will be summarized descriptively at Weeks 24, 48, and 60. For the total score of SGRQ at Week 24, the difference in the change from baseline between the treatment groups will be provided using an analysis of covariance (ANCOVA) model. The baseline total score will be used as covariate in the analysis.

5.4.2.2.7. Lung function parameters

The change from baseline of each lung function parameter will be descriptively summarized by visit.

5.5. Tertiary/Exploratory Endpoints Analysis

5.5.1. Definition of Endpoint

QOL-B NTM module

The QOL-B respiratory symptom domain and NTM module will be assessed in this study. The respiratory symptom domain consists of 9 items. The NTM module is developed specifically for NTM symptoms and consists of NTM symptoms (7 items), body image (4 items), digestive symptoms (6 items), and eating problems (3 items). The NTM symptoms domain includes the following items: feverish (chills, sweating), sensitivity to smell, sensitivity to taste, memory problems, bad taste in mouth, bothered by cold weather, problems sleeping. Responses are measured using a 4-point Likert Scale (eg, "a lot", "a moderate amount", "a little", or "not at all"). Individual domain scores are calculated, scaled from 0 to100 (100=best HRQOL).

5.5.2. Analysis Methods

The following endpoints will be descriptively summarized and listed. No imputation rules will be applied for withdrawn and missing data.

- The domain scores of QOL-B NTM module and the changes from baseline at Weeks 24, 48, and 60.
- Rate of culture reversion (relapse or reinfection) in MIGIT up to Week 60. The denominator is defined as the number of subjects with sputum culture conversion before Week 60 and the numerator is defined as the number of subjects with at least one positive culture up to Week 60 after the culture conversion.
- Distribution of MICs to BDQ, RFP, RBT, EB, CAM, AMK and SM.
- Percentage of participants having MAC isolates with acquired resistance to CAM (MIC ≥32 μg/mL) detected by a phenotypic method up to Week 60.
- Percentage of participants having MAC isolates with increased MICs to BDQ (at least 4-fold increase) up to Week 60
- For participants who achieved sputum culture conversion, the changes from baseline in the total score of SGRQ, the domain scores of QOL-B NTM module, and chest CT findings

5.6. Safety Analyses

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity (end of study/early withdrawal).

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified. All summaries will be descriptive, and no inferential methods will be used to compare intervention arms for safety.

Safety and tolerability will be assessed by evaluating treatment emergent-adverse events (TEAEs), ECGs, physical examinations, vital signs measurements, clinical laboratory tests, pregnancy testing, and management of common expected toxicities.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who receive each study intervention will be summarized.

Descriptive statistics of each study intervention (N, mean, SD, median, and range [minimum, maximum]) will be summarized for total duration, total number of treatment and total dose.

The number (%) of participants with a switch to individualized treatment regimen will be summarized by intervention group under investigation phase and optional investigation phase. .

Study intervention duration (weeks) is defined as (date of last dose of study intervention – date of first dose of study intervention +1) / 7.

Study intervention compliance will be summarized descriptively. See Appendix 7 for further details.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 27.1). Any AE occurring at or after the initial administration of study intervention through the end date of investigation phase defined in Section 5.1 is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events (TEAE) will be included in the analysis of investigation phase and optional investigation phase. All reported adverse events will be included in the analysis of follow-up phase. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group and analysis phase.

Summary tables will be provided for treatment-emergent adverse events, all adverse events will be presented in a descending order by incidence based on all participants (Total column):

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study intervention
- AEs by severity
- AEs by relationship to study intervention
- AEs leading to dose interruption/dose modification of the study intervention
- AEs by onset time (at 3-months interval)

In addition to the summary tables, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of study intervention/termination of study participation

Incidence of other treatment-emergent adverse events of special interest will be summarized by intervention group and analysis phase. See Appendix 8 for list of adverse events in each category.

Deaths will be displayed by actual intervention received. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death
- Relationship to study intervention (yes/no)

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics (n, mean, SD, minimum, median and maximum) and graphical displays will be presented for chemistry, hematology, and urinalysis laboratory tests at scheduled time points by intervention arm and study phase.

Change/percent change from baseline to each scheduled time point will be summarized for chemistry, hematology, and urinalysis tests and displayed by intervention group.

An abnormality (toxicity grade and/or abnormality based on normal ranges) will be attributed to the baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For toxicity grades, treatment emergent (TE) will be concluded if the postbaseline value is worse than the baseline value.
- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Number and percentage of participants with clinically important laboratory values and/or markedly abnormal values (defined as grade 3 or higher) will be presented by intervention group over time. Listing of clinically important laboratory values will be defined according to DMID definitions.

Plots of mean (+/-SE) values and changes from baseline over time for clinically important laboratory parameters will be presented by intervention arm and analysis phase.

Shift tables will be provided summarizing the shift in laboratory values from baseline over time with respect to abnormality criteria (low, normal, high).

Descriptive statistics by toxicity grade over time will be presented. Shift summaries from baseline toxicity grade to the worst toxicity grade will also be presented.

Shift summaries from baseline laboratory value to the worst grade in chemistry and hematology tests with will be presented.

5.6.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, respiratory rate, weight, pulse, blood pressure (systolic and diastolic) will be summarized at each assessment time point. Change/Percent change from baseline will be summarized for the intervention arm and analysis phase. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered TE if they meet both value and change criteria in the table below.

For criteria that do not include an increase or decrease from baseline:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Incidence of vital signs during intervention, as defined in Table 5, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. A listing of participants with treatment-emergent vital signs will be presented, along with a listing of all vital sign measurements.

Physical examinations including visual/audiology tests are summarized in frequency tables.

Table 5: Clinically Important/Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	>[120] bpm and with >[30] bpm increase from baseline
	<[50] bpm and with >[20] bpm decrease from baseline
Systolic blood pressure	>[180] mm Hg and with >[40] mm Hg increase from baseline
	<[90] mm Hg and with >[30] mm Hg decrease from baseline
Diastolic blood pressure	>[105] mm Hg and with >[30] mm Hg increase from baseline
	<[50] mm Hg and with >[20] mm Hg decrease from baseline
Temperature	>[38]ºC and with >=[1]ºC increase from baseline
Respiratory rate	>[20] breaths per minute
Weight	increase [10%] kg from baseline
	decrease [10%] kg from baseline

5.6.3.3. Electrocardiogram

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the correction method, Bazett's formula (QTcB), Fridericia's formula (QTcF).

Bazett's formula: QTcB (msec) = QT (msec) / (RR (msec)/1000)$^{1/2}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/2}$

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$.

For the time points on which triplicate ECGs apply, a rounded mean value to the nearest integer per triplet will be calculated per time point before any further handling. This round mean value will be used through the entire analysis also in case of 1 or 2 missing values.

ECG records with partial dates (any of day/month/year is missing) will not be used in analysis except in the listings.

If heart rate (HR) is missing, it will be calculated using RR (if available) and rounded to the integer value (see the formula below) before any further handling if applicable.

$$\frac{1000}{RR(ms)} = \frac{HR(bmp)}{60}$$

HR from the vital signs section (ie, pulse) will not be used in this ECG analysis section. RR values (if applicable) will only be listed. Recalculated HR values will be flagged.

The number and percentage of participants with QTc interval will be summarized at each scheduled time point. The number and percentage of participants with QTc interval increases from baseline to the maximum postbaseline value will be summarized. Refer to the following table for summary categories.

Criteria for Abnormal QTc Values and Changes from Baseline	
QTcF/QTcB value	<=450
	>450 – 480
	>480 – 500
	>500
QTcF/ QTcB change from baseline	<=30
	>30 – <=60
	> 60

A shift table will be provided summarizing the shift from baseline to maximum QTc interval classification over time

Descriptive statistics of ECG parameters and change/percent change from baseline will be summarized at each scheduled time point.

If ECG measurements are repeated at a visit, they will be averaged. The averaged value will be considered the 'Visit' ECG result.

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

The number and percentage of participants with treatment-emergent ECG values will be presented by intervention group in analysis phase over time:

- Heart rate (bpm): [<50] and [>100]
- PR interval (msec): [<120] and [>200]
- RR interval (seconds): [<0.6] and [>1.2]
- QRS interval (msec): [>120]
- QTcF/ QTcB (msec): [>500]

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time.

Listings will be produced for all ECG data including unscheduled visit data. A listing of clinically relevant ECG abnormalities will also be provided.

5.6.3.4. Pregnancy testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. A listing of participants who pregnancy will be provided

5.7. Other Analyses

5.7.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set, defined as participants who have received at least 1 dose of any study intervention and have at least 1 valid blood sample drawn for PK analysis.

All plasma concentrations below quantification limit (BQL) or missing data will be labeled as such in the concentration data presentation. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

5.7.1.1. Statistical Analysis of Pharmacokinetics: (Descriptive Statistics)

Descriptive statistics (N, mean, standard deviation, %CV, median, minimum and maximum) will be calculated to summarize plasma BDQ, M2, CAM and 14-OH-CAM concentrations at each sampling time point by intervention group and study day (Day 1, Weeks 2, 8, 12, 24, and 48 [For

Week 48, BDQ and M2 only]). Subjects will be excluded from the PK analysis if their data did not allow for accurate assessment (eg, incomplete administration of the study drug; missing information of dosing and sampling times).

For descriptive statistics of the plasma BDQ, M2, CAM and 14-OH-CAM concentrations, following data handing rules will be applied:

- Data from samples outside Visit window rule and Time window rule specified in Table 2 and Table 6 will be excluded in the calculation.
- BQL will be substituted with "0 (zero)".
- Number of plasma concentration data will be calculated based on the number of subjects with measurable value including BQL.
- When more than half (>50%) of plasma concentration are BQL at each scheduled time point, mean, median, and minimum will be shown as "BQL", and SD, and %CV will be shown as "NC" (not-calculated), respectively. If all plasma concentrations are BQL, maximum will also be shown as "BQL".
- When number of plasma concentration data is equal to or less than 2, only N and mean will be calculated and SD, %CV, median, minimum and maximum will be shown as "NC" regardless of the proportion of BQL, respectively.
- If the dose level is modified from the initially planned dose or prior to blood sampling day, plasma concentration data for that day will be excluded from the descriptive statistics.

Table 6: Pharmacokinetic sampling time per Protocol and for analysis

	Nominal time (Analysis time point) (h)	(min)	Time window (min)
Predose	0	0	Before dosing at the visit
Postdose	3	180	96 - 288

The plasma BDQ, M2, CAM and 14-OH-CAM concentrations will be tabulated and summarized by intervention group, respectively. Individual concentrations will be listed.

5.7.1.2. Population Pharmacokinetic Analysis

Population PK (popPK) analysis of plasma concentration-time data of BDQ (and M2, if needed) will be performed with nonlinear mixed-effects modeling (NONMEM) approach. If deemed necessary, data will be combined with data from other studies. Details will be given in a population PK analysis plan and the result will be presented in a separate report.

In the popPK analysis, based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters (C_{max}, C_{trough} [trough concentration], AUCτ) of BDQ at Day 1, Weeks 2, 8, 12, 24, and 48 will be derived. If deemed necessary, a similar analysis for C_{max}, C_{trough}, AUCτ will be performed for M2.

Descriptive statistics (N, mean, standard deviation, %CV, median, minimum and maximum) will be calculated to summarize PK parameters of TMC207 (and M2, if needed) at Day 1, Weeks 2, 8, 12, 24, and 48.

For descriptive statistics of the PK parameters of BDQ (and M2, if needed) from population pharmacokinetics, following parameters will be reported.

- C_{max}, C_{trough} and AUCτ

The PK parameters of BDQ (and M2, if needed) will be tabulated and summarized at Day 1, Weeks 2, 8, 12, 24, and 48, respectively.

5.7.1.3. Generating Pharmacokinetic Profiles

The following graphs will be produced by intervention group:

- Boxplots of the BDQ concentration at predose and 3 hours postdose (Day 1, Weeks 2, 8, 12, 24, and 48), respectively.
- Boxplots of the M2 concentration at predose and 3 hours postdose (Day 1, Weeks 2, 8, 12, 24, and 48), respectively.
- Boxplots of the CAM concentration at predose and 3 hours postdose (Day 1, Weeks 2, 8, 12 and 24), respectively.
- Boxplots of the 14-OH-CAM concentration at predose and 3 hours postdose (Day 1, Weeks 2, 8, 12 and 24), respectively.

5.7.2. Pharmacokinetic/Pharmacodynamic Relationships

PK/PD analyses will be performed on the collected data when all participants have reached Week 24 or discontinued earlier. The PK/PD analyses may be performed at earlier time points as necessary to support efficacy and safety findings.

The PK/PD analysis will be based on the PK/PD analysis set (defined in Section 4) for nominal time-matched plasma concentrations and safety parameters.

Safety parameter: QTcF

- 3 hours postdose at each visit on Day 1, Weeks 2, 8, 12, 24, and 48

The following plots will be generated to evaluate the relationship between safety parameter (absolute value and change from baseline for QTcF) and plasma concentrations of BDQ, M2, CAM and 14-OH-CAM, respectively:

- QTcF at each time-matched point of measurement from each intervention group (for BDQ, and M2, Treatment A only) will be plotted against the corresponding plasma concentration of BDQ, M2, CAM and 14-OH-CAM, respectively.
- Additional plots will be produced, if deemed necessary.

Pearson product moment correlations (R^2) will be calculated for nominal time-matched plasma concentrations and safety parameter.

Population PK/PD (selected efficacy endpoints and selected AEs as additional PD parameters) analysis may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. Details will be given in a PK/PD analysis plan will be presented in a separate report.

5.8. Interim Analyses and Data Monitoring Committee (DMC) Review

5.8.1. Interim Analysis

Interim futility analysis will be conducted at the time when the first 60 randomized subjects have completed Week 24 visit or ended study participation or switched to individualized treatment regimen before Week 24 visit. This futility analysis is nonbinding and the IDMC will recommend the continuation or termination of the study based on the whole package of information, which also includes other efficacy and safety assessments.

The primary analysis will be conducted at the time when all participants have completed Week 24 or discontinued earlier.

After the primary analysis, IAs are planned when:

- All participants have reached Week 48 or discontinued earlier or have switched to the optional cohort
- All participants have reached Week 60 or discontinued earlier or have switched to the optional cohort

The final analysis will be performed when all participants have completed the last study visit or discontinued earlier.

This SAP covers the definitions of analysis sets, derived variables and statistical methods for the primary analysis, interim analyses after the primary analysis and final analyses of this study. For the interim futility analysis, the detailed analysis including the definitions of analysis sets, derived variables and statistical methods are documented in IDMC SAP.

5.8.2. Data Monitoring Committee (DMC) Review

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study and to meet efficacy objectives. This committee will consist of at least one medical expert in the relevant therapeutic area, at least one medical expert in cardiology, and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review safety and efficacy data and results. After the review of the interim (futility) analysis results at Week 24, the IDMC will make recommendations regarding the continuation of the study.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BDQ	Bedaquiline
CAM	Clarithromycin
CI	confidence interval
C_{max}	maximum concentration
CRF	case report form
CV	coefficient of variation
DMC	Data Monitoring Committee
DMID	division of microbiology and infectious diseases
EB	Ethambutol
ECG	electrocardiogram
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FU	follow-up
IQ	interquartile
MAC-LD	mycobacterium avium complex-lung disease
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQs	standardised MedDRA queries
SOC	standard of care
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

The per-protocol analysis set defined in the protocol will not be used for analysis.

6.3. Appendix 3 Demographics and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be presented by intervention arm and overall for the ITT analysis set. Continuous variables will be summarized by descriptive statistics including the number of participants, mean, standard deviation, median, range and interquartile range. Categorical/binary variables will be summarized by counts and percentages.

Table 7 and Table 8 present demographic variables and baseline characteristics that will be summarized by intervention group and overall for the ITT analysis set.

Table 7: Demographic Variables

Continuous Variables:	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Categorical Variables	
Age (<60 years, >=60 to <70 years and >=70 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Region [Japan, non-Japan]	

Table 8: Baseline characteristics

Continuous Variables:	**Summary Type**
Duration of previous therapy for MAC-LD (yr) ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Categorical Variables	
MAC species (M.avium, M.intracellulare, M.avium+M.intracellulare)	Frequency distribution with the number and percentage of participants in each category.
Previous therapy for MAC-LD (CAM, AZM, EB…)	
Number of previous therapies for MAC-LD (1, 2, 3, 4, ≥5)	
Duration of previous therapy for MAC-LD (<24 months, >=24 to <36 months, >=36 months)	

6.4. Appendix 4 Protocol Deviations

Only major protocol deviations will be summarized. Protocol deviations and violations will be based on clinical review, but not limit to. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Entered but did not satisfy inclusion/exclusion criteria
- Received an excluded concomitant treatment
- Efficacy assessment deviation
- Received wrong treatment or incorrect dose
- Other

All major protocol deviations will be tabulated by coded term by intervention arm for the ITT analysis set. A listing of the major protocol deviations will also be presented.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention. Medication that started before Day 1 and continued afterwards will be summarized both as prior and, separately, as concomitant medication.

Summaries of prior and concomitant medications will be presented by ATC term and preferred term by intervention group. The proportion of participants who receive each concomitant medication will be summarized by analysis phase as well as the proportion of participants who receive at least 1 concomitant medication.

6.6. Appendix 6 Medical History

A tabulation of the general medical history coded terms will be provided by body system class and by intervention arm.

6.7. Appendix 7 Intervention Compliance

Compliance will be summarized descriptively for each study intervention. Compliance to randomized intervention versus actual intervention will be presented in a summary table.

The average of percentage of treatment compliance will be summarized by intervention group in the investigation phase and the optional investigation phase.

Compliance will be calculated as follows:

Compliance (%) = 100 x number of days taking study intervention/number of days of planned study intervention intake

Subjects with 80% or more compliance will be considered compliers.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined using SMQ (MedDRA version 27.1) as follows:

- Acute pancreatitis (narrow and broad B terms)
- Rhabdomyolysis/myopathy (narrow A terms)
- Severe cutaneous adverse events (narrow and broad terms)
- Torsade de pointes/QT prolongation (narrow and broad terms)
- Hepatic disorders (selected sub-SMQs) shows:
  - All narrow and broad terms of Cholestasis and jaundice of hepatic origin SMQ
  - All narrow terms of Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ
  - All narrow terms of Hepatitis, noninfectious SMQ
  - All narrow terms of Liver related investigations, signs and symptoms SMQ
  - All narrow terms of Liver-related coagulation and bleeding disturbances SMQ

6.9. Appendix 9 Medications of Special Interest

Not applicable.

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on DMID and defined as follows.

Hematology

	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 - 10.5 gm/dL	8.0 - 9.4 gm/dL	6.5 - 7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1000 - 1500 /mm3	750 - 999 /mm3	500 - 749 /mm3	<500 /mm3
Platelets	75,000 - 99,999 /mm3	50,000 - 74,999 /mm3	20,000 - 49,999 /mm3	<20,000 /mm3
White Blood Cell (WBC) Count	11,000 - 13,000 /mm3	13,000 - 15,000 /mm3	15,000 - 30,000 /mm3	>30,000 or <1,000 /mm3
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26 - 1.5 x ULN	1.51 - 3.0 x ULN	>3 x ULN

Chemistry

	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130 - 135 mEq/L	123 - 129 mEq/L	116 - 122 mEq/L	<116 mEq/L
Hypernatremia	146 - 150 mEq/L	151 - 157 mEq/L	158 - 165 mEq/L	>165 mEq/L
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L	<2.0 mEq/L
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	>7.0 mEq/L
Hypoglycemia	55 - 64 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	<30 mg/dL
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL	>500 mg/dL
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	<6.1 mg/dL
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	>13.5 mg/dL
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	<0.6 mEq/L
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL	1.0 - 1.4 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
Hyperbilirubinemia (with Grade 1 or more AST, ALT or ALP)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	>1.75 x ULN
Hyperbilirubinemia (with normal AST, ALT and ALP)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 - 3.0 x ULN	>3.0 x ULN
Blood urea nitrogen (BUN)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	>10 x ULN
Hyperuricemia (uric acid)	7.5 - 10.0 mg/dL	10.1 - 12.0 mg/dL	12.1 - 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	>6 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	>8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	>5.1 x ULN

Urinalysis

	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+	2-3+	4+	NA

6.11. Appendix 11 Unblinding Plan

This unblinding plan details who will be unblinded to the microbiological result data and the documentation of unblinding until the completion of the primary analysis.

The default unblinders are as follows.

- Site Manager
- Local Trial Manager
- Global Trial Lead (GTL)
- Clinical Trial Manager (CTM)
- Clinical Trial Assistant
- Clinical Research Manager
- Vendor manager for Central lab

Default unblinders are required to give their consent (Appendix 12) to declare not to disclose any microbiological result data to any non- unblinders to maintain the data integrity of this trial. The GTL/CTM will keep a running log (Appendix 13) of personnel who have been unblinded to microbiological result data and the date of their consent.

Any sponsor personnel other than the above default unblinders will not have access to microbiological result data after Week 2 until unblinding takes place for the primary analysis except for the investigator's decision related to therapy based on microbiological result (e.g. transfer to optional cohort, individualized treatment regimen, or follow-up period).

6.12. Appendix 12 Agreement on the Unblinded Information Handling

TMC207NTM3002 study is a multicenter, randomized, open-label, active-controlled study. The primary analysis of this study will be carried out after all participants have reached Week 24 or have discontinued earlier than Week 24.

As this is an open-label study, blinding procedures are not applicable. However, the microbiological results from Week 2 to Week 24 will be blinded to the investigators, site staffs and participants until the completion of the other assessments at Week 24 by the investigators. In order to maintain the blind, the investigator should not perform microbiological tests for acid-fast bacillus at the study site after Day 1 until completion of the assessments other than microbiological assessments at the Week 24 except in emergency situations related to subject safety or chemotherapy. In case the investigators need to know the microbiological result to decide if participants should be switched to an individualized treatment regimen or continue the study treatment regimen, due to clinical worsening, the investigators can access the microbiological result from the central laboratory (for the detailed procedure, refer to the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test). Sponsor except for specific personnel listed below must keep the blinding of all the microbiological assessment after Week 2 until unblinding takes place for the primary analysis except for the investigator's decision related to therapy based on microbiological result (e.g. transfer to optional cohort, individualized treatment regimen, or follow-up period).

In addition, sponsor personnel involved in monitoring of the study sites and personnel involved in management operation of the central laboratory etc. are excluded from maintenance of blinding for microbiology assessments, taking into account that sponsor needs to confirm that investigators and etc. comply with the protocol and the decision to switch to individualized treatment regimen and the optional cohort is made based on the appropriate process.

The access to the unblinded microbiology result data will be strictly limited to the default unblinders who have signed this agreement. A list of all default unblinders will be provided by the GTL/CTM. To be a default unblinders of this study, you need to fully understand the above and agree as follows:

- Not sharing any microbiological result data from Week 2 until unblinding takes place for the primary analysis with other than the default unblinders in any manner.
- Not printing any microbiological result data from Week 2 until unblinding takes place for the primary analysis.
- Immediately reporting any potential deviations from this agreement occurred in any default unblinders to the GTL/CTM of this study.
- Immediately reporting to the GTL/CTM of this study if any existing default unblinder is replaced by other responsible personnel.

This agreement shall become effective from the date of its signature and remain valid until the completion of the primary analysis.

I consent to take special care to protect the integrity.

(Signature)

6.13. Appendix 13 Running Log of Default Unblinders

Affiliation/Company	Function/ Department	Role	Name	Email address	Start date (Agreement signed date)	End date

7. REFERENCES

Griffith DE (2018), Eagle G, Thomson R, et al. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT): a prospective, open-label, randomized study. Am J Respir Crit Care Med. 2018;198(12):1559-1569.

Olivier KN (2017), Griffith DE, Eagle G, et al. Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung Disease. Am J Respir Crit Care Med. 2017;195(6):814-823.